Articles

Total Synthesis of Bao Gong Teng A, a Natural Antiglaucoma Compound

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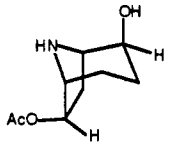
The total synthesis of Bao Gong Teng A (1), a novel natural product which shows strong antiglaucoma properties, is described. The key step involves the highly regioselective and somewhat stereoselective 1,3-dipolar cycloaddition of acrylonitrile to *N*-benzyl-3-hydroxypyridinium bromide **2** to give the easily separable crystalline exo and endo diastereomers **3x** and **3n** in yields of 54% and 36%, respectively. Catalytic hydrogenation of the enone of **3x** followed by reduction with sodium borohydride gave, via the saturated ketone **4**, the exo alcohol **5x** in 54% overall yield along with a small amount of the endo stereoisomer **5n**. Protection of the alcohol followed by addition of methyl Grignard produced, after hydrolysis of the intermediate imine and the silyl ether, the desired 6-*exo*-acetyl-8-benzyl-8-azabicyclo[3.2.1]octan-2-*exo*-ol (**8**) in 71% yield. The synthesis of Bao Gong Teng A (**1**) was completed by first effecting a Baeyer–Villiger oxidation of **8** to give *N*-benzyl Bao Gong Teng A (**9**) (54% yield) and then cleaving the *N*-benzyl group by hydrogenolysis to produce **1** in 74% yield, thereby ending an eight-step synthesis of Bao Gong Teng A (**1**) in 8% overall yield from readily available starting materials.

Bao Gong Teng A is an alkaloid isolated from a Chinese herb, *Erycibe obtusifolia* Benth, which has been used for the treatment of fever in humans but which has very strong side effects.[1] Its structure was shown to be 6-*exo*-(acetyloxy)-8-azabicyclo[3.2.1]octan-2-*exo*-ol (**1**)[2-5] and its absolute configuration recently determined to be as shown.[5]



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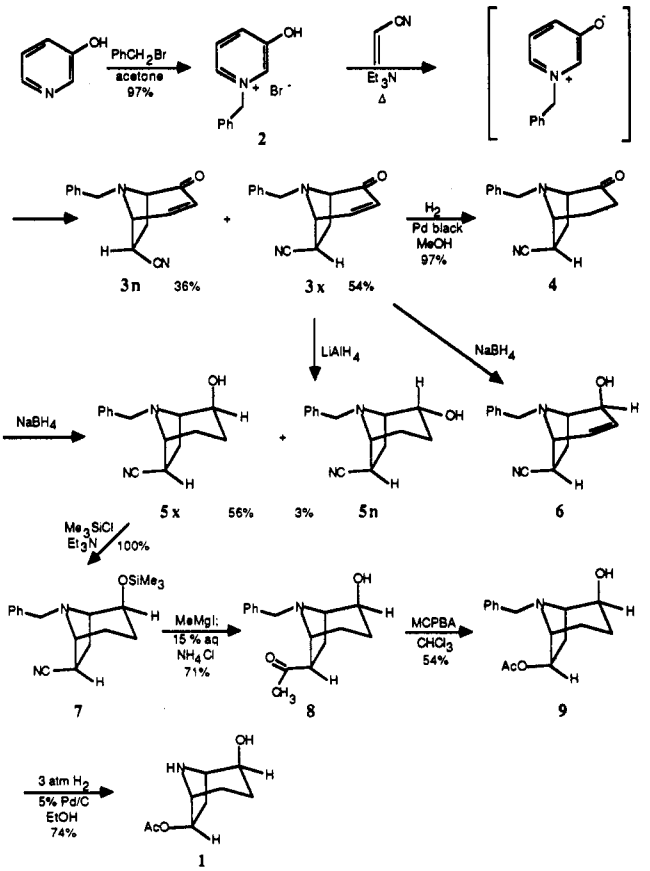
Other compounds have also been isolated from Chinese herbs that have similar structures and biological activity.[6-8] Later, it was found that, when used as eyedrops, Bao Gong Teng A was more effective and had fewer side effects than pilocarpine and physostigmine in curing glaucoma.[2-5,9-12]

Scheme I



The clinical practice of this eyedrop treatment has been severely limited due to scarcity of the required herbs.[1,13,14]

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Because of this limitation, the synthesis of this compound has been a target of considerable interest. Compound 1 is very sensitive to both acid and base, thereby causing great potential difficulty in its synthesis. At the beginning of the work described herein, although several groups had been interested in a synthesis of 1, there had been no reports of success in its preparation. Since the completion of our synthesis, one other synthesis has been reported,[15] namely the conversion of 6-*exo*-(acetyloxy)tropanone (itself prepared in four steps from furan by Robinson's method)[16] into 1 in seven steps. We report here the very short total synthesis of this natural product Bao Gong Ten A (1).

The route we designed for the total synthesis of compound 1 proceeded via the sequence of reactions shown in Scheme I. The 1,3-dipolar cycloaddition of pyridinium betaines is a very useful method for preparing 8-azabicyclo[3.2.1]octane (isotropine) derivatives.[17] Reaction of the readily available *N*-benzyl-3-hydroxypyridinium bromide 2 (prepared in 97% yield by alkylation of pyridin-3-ol with benzyl bromide) with acrylonitrile gave a mixture of diastereomers **3x** and **3n** as reported by Katritzky, but no information on the separation of this mixture was given.[18] We repeated this experiment and, after chromatography on a silica gel column, were able to obtain the diastereomerically pure crystalline compounds **3x** (mp 90–91 °C) and **3n** (mp 42.5–43.0 °C) in yields of 54% and 36%, respectively. Thus, the desired exo isomer **3x** is the major isomer in this cyclization. We now had to devise a method for its reduction to give the 2-*exo* alcohol **5x**.

Several routes were examined to obtain the desired alcohol **5x**. The one which produced the correct stereoisomer **5x** in high yield as the major product required two steps. First the enone **3x** was hydrogenated at room temperature and under atmospheric pressure using palladium black as catalyst (prepared from palladium chloride by reduction with sodium borohydride)[19] to give the saturated ketone 4 in 97% yield. In a second step, this ketone was then reduced using sodium borohydride to afford **5x** and its stereoisomer **5n** in yields of 56% and 3%, respectively. Thus, the overall yield of the desired compound **5x** for the two steps was 54%. Other methods were less successful. For example, Brown and Hess have reported the use of sodium borohydride to reduce unsaturated ketones to saturated alcohols with good stereoselectivity.[20] However, when the enone **3x** was treated with sodium borohydride directly, the main product was the unsaturated 2-*exo*-hydroxy compound **6**. Reduction of **3x** using lithium aluminum hydride produced mainly the 2-*endo*-hydroxy compound **5n**. The exo alcohol **5x** showed a strong, sharp absorption in its infrared spectrum at 3500 cm^{-1} while the endo isomer **5n** showed a broad one. The melting points of these two compounds were 71 and 139.0 °C, respectively. Consideration of these two points suggested that the alcohol **5x** has an intramolecular hydrogen bond, which requires the hydroxyl group in **5x** to be in the desired β-configuration.

To complete the synthesis, we needed to convert the nitrile into an acetoxy group with retention of configuration and remove the *N*-benzyl protecting group. A resonable approach would involve first conversion of the nitrile into a methyl ketone followed by a Baeyer–Villiger oxidation to give the acetate and final hydrogenolysis. We therefore first protected the secondary alcohol as its trimethylsilyl ether **7**, prepared in quantitative yield by the usual method. Addition of methylmagnesium iodide to **7** produced the intermediate imine.[21] In general, hydrolysis of imines, obtained from the reaction of a Grignard reagent with a nitrile, is carried out with hydrochloric acid.[22] However, due to the potential sensitivity of compound such as **5x** to acid and base, we used instead a solution of 15% aqueous ammonium chloride to obtain the desired 6-*exo*-acetyl-8-benzyl-8-azabicyclo[3.2.1]octan-2-*exo*-ol (**8**) in 71% yield. The trimethylsilyl protecting group was also cleaved off under these hydrolytic conditions. *N*-Benzyl Bao Gong Teng A (**9**) was obtained by effecting the Baeyer–Villiger oxidation using *m*-chloroperbenzoic acid in chloroform in 54% yield. The infrared spectrum of **9** showed a carbonyl absorption at 1725 cm^{-1} indicative of the ester as compared to the absorption of 1702 cm^{-1} for the ketone in **8**. Also the appearance of a multiplet in the ^1H NMR spectrum at δ 5.00–5.20 was consistent with the presence of the secondary acetate. Finally the synthesis of Bao Gong Teng A (1) was completed when the *N*-benzyl group of **9** was cleaved by catalytic hydrogenation in ethanol over 5% Pd/C using 3 atm of hydrogen to produce 1 in 74% yield.

In summary, we have been able to carry out the total synthesis of the naturally occurring antiglaucoma compound, Bao Gong Teng A (1), in only eight steps and 8% overall yield from readily available starting materials, using as the key step the 1,3-dipolar cycloaddition of a pyridinium betain and acrylonitrile. Further synthetic work and the testing of intermediates is currently being carried out.

Experimental Section

General. ^1H NMR spectra were taken at 90 MHz using deuteriochloroform as solvent. Analytical thin-layer chromatographic (TLC) analyses were performed by using precoated silica gel or alumina oxide plates. Melting points are uncorrected.

1-Benzyl-3-hydroxypyridinium Bromide (2). To a solution of 3-hydroxypyridine (10 g, 0.105 mol) in 200 mL of acetone was added benzyl bromide (12.5 mL, 0.105 mol). The solution was seeded (with crystals of **2** made previously) and kept at room temperature overnight. The mixture was filtered, and 24.8 g of dry yellow crystals were obtained. Anhydrous ether (50 mL) was added, and the filtrate was allowed to stand overnight to give a second crop of crystals, bringing the total amount of **2** collected to 26.8 g (97% yield): mp 127–130 °C.

8-Benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-*exo*-carbonitrile (3x) and 8-Benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-*endo*-carbonitrile (3n). A mixture of the pyridinium salt **2** (20 g, 75.7 mmol), 150 mL of freshly purified acrylonitrile, triethylamine (21 mL), and a small amount of hydroquinone was refluxed under a dry nitrogen atmosphere for 20 h. Removal of the solvent under reduced pressure gave a brown residue, which was diluted with water and extracted with CH_2Cl_2. Evaporation of the solvent gave 19.9 g of a residue, which was purified by column chromatography on silica gel, eluting with 2:3 ether/hexane. The endo nitrile **3n** (6.4 g, 35.5%) eluted first and then the exo nitrile **3x** (9.8 g, 54.4%). The endo nitrile **3n** could be crystallized from acetone, mp 42.5–43.0 °C: ^1H NMR δ 7.16–7.26 (5 H, m), 7.00 (1 H, dd, J = 11.2, 6.2 Hz), 6.25 (1 H, dd, J = 11.2, 1.4 Hz), 3.92 (1 H, t, J = 5.6, 6.2 Hz), 3.65 (2 H, s), 3.55 (1 H, d,

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J = 8.4 Hz), 3.34 (1 H, ddd, J = 11.2, 5.6, 5.3 Hz), 2.80 (1 H, ddd, J = 15.5, 11.2, 8.4 Hz), 1.90 (1 H, dd, J = 15.5, 5.6 Hz); IR (KBr) 2245, 1696 cm^{-1}; MS (m/z) 238 (M^+), 185. The exo nitrile **3x** could be crystallized from methanol, mp 90–91 °C: ^1H NMR δ 7.26–7.38 (5 H, m), 6.92 (1 H, dd, J = 11.0, 5.1 Hz), 6.16 (1 H, d, J = 11.0 Hz), 4.02 (1 H, d, J = 5.1 Hz), 3.84 (2 H, s), 3.68 (1 H, d, J = 8.7 Hz), 3.00 (1 H, dd, J = 9.0, 3.0 Hz), 2.69 (1 H, ddd, J = 15.4, 9.0, 3.0 Hz), 2.13 (1 H, dd, J = 15.4, 9.0 Hz). IR and MS are the same as **3n**.

8-Benzyl-2-oxo-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (4). To a stirred suspension of $PdCl_2$ (0.013 g, 0.007 mmol) in 20 mL of methanol was added sodium borohydride (0.057 g, 1.5 mmol) in portions, and the mixture was kept at room temperature for 10 min. The granular deposit of palladium black is separated by decantation and wshed several times with methanol. A solution of **3x** (9.3 g, 39 mmol) in 150 mL of methanol was added to the catalyst prepared above and subjected to catalytic hydrogenation at room temperature at atmospheric pressure for 20 h. The palladium black was filtered off and washed with methanol and the filtrate evaporated to give **4** (9.1 g, 97% yield) as white crystals, mp 86.5–87.0 °C: ^1H NMR δ 7.26–7.39 (5 H, m), 3.85 (2 H, s), 3.80 (1 H, m), 3.68 (1 H, d, J = 8.7 Hz), 3.00 (1 H, dd, J = 8.9, 3.1 Hz), 2.69 (1 H, ddd, J = 15.4, 8.9, 3.1 Hz), 2.13 (1 H, dd, J = 15.4, 8.9 Hz), 1.84–1.90 (4 H, m); IR (KBr) 2243, 1718 cm^{-1}; MS (m/z) 241 (M^+ + 1).

8-Benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (5x) and 8-Benzyl-2-*endo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (5n). Sodium borohydride (9.0 g, 238 mmol) was added at 25 °C in portions with stirring to a solution of **4** (9.3 g, 38.7 mmol) in 150 mL of methanol, and the mixture was stirred for 2 h. Evaporation of the solvent under reduced pressure afforded a residue to which water was added. The mixture was extracted with ether and dried over sodium sulfate. Evaporation of the solvent gave 8.05 g (88% crude yield) of a residue, which was chromatographed on alumina, eluting with 2:3 $CHCl_3$/hexane. The desired exo alcohol **5x** (5.25 g, 56%) was obtained first as pure colorless needles followed by **5n** (0.3 g, 3%) as an oil. The ratio of **5x** and **5n** was 94:6. Exo alcohol **5x**: mp 71.0–72.0 °C; ^1H NMR δ 7.28–7.39 (5 H, m), 3.80 (2 H, s), 3.65 (1 H, m), 3.40 (1 H, m), 3.30 (1 H, m), 2.88 (1 H, m), 2.69 (1 H, ddd, J = 15.4, 8.8, 3.1 Hz), 2.13 (1 H, dd, J = 15.4, 8.9 Hz), 1.60 (1 H, exchangeable, s), 1.34–1.90 (4 H, m); IR (KBr) 3500 (s), 2320 cm^{-1}; MS (m/z) 243 (M^+ + 1), 225, 165, 151, 91. Endo alcohol **5n**: mp 139.0–139.5 °C; IR (KBr) 3500, 2320 cm^{-1}; MS (m/z) 243 (M^+ + 1), 225, 91.

8-Benzyl-2-*exo*-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (7). A solution of trimethylsilyl chloride (7.8 mL, 6.67 g, 61.5 mmol) in 20 mL of anhydrous ether was added dropwise at 25 °C with stirring to a solution of **5x** (5.0 g, 20.66 mmol) in anhydrous ether under N_2. To this solution was added dropwise a solution of 9.7 mL of triethylamine in anhydrous ether. The solution was stirred at 25 °C for 5 h, water was added, and the aqueous layer was extracted with ether. The combined organic extract was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 6.5 g of **7** (100% yield) as white crystals, mp 90.5–91.0 °C.

1-[8-Benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]oct-6-*exo*-yl]ethanone (8). A solution of iodomethane (9.3 mL, 65.5 mmol) in anhydrous ether was added with stirring under N_2 to magnesium ribbon (3.50 g, 144 meq) and 30 mL of sodium dried ether. When all of the magnesium ribbon had dissolved, a solution of the trimethylsilyl ether **7** (4.6 g, 14.6 mmol) in 100 mL of anhydrous ether was added dropwise and the mixture stirred for 10 h. After that time, 100 mL of 15% NH_4–H_2O was added dropwise and the mixture stirred for 2 h at 25 °C and then extracted with diethyl ether. The combined organic extract was washed with water and dried over sodium sulfate. Evaporation of the solvent and chromatography on alumina, eluting with 2:3 CH_2Cl_2/hexane, gave **8** as white crystals (2.70 g, 71% yield), mp 101.5–102.5 °C: ^1H NMR δ 7.25–7.34 (5 H, m), 3.42 (2 H, s), 3.40–3.80 (2 H, m), 3.30 (1 H, m), 2.40–3.00 (2 H, m), 2.22 (3 H, s), 2.12–2.30 (1 H, m), 1.62 (1 H, s), 1.40–2.00 (4 H, m); IR (KBr) 1702 cm^{-1}; MS (m/z) 260 (M^+ + 1), 215, 136, 91. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 73.99; H, 8.37; N, 5.15.

8-Benzyl-6-*exo*-(acetyloxy)-8-azabicyclo[3.2.1]octan-2-*exo*-ol (9). To a solution of **8** (1.0 g, 3.86 mmol) in $CHCl_3$ at 25 °C was added *m*-chloroperbenzoic acid (0.90 g, 5.2 mmol) in $CHCl_3$. The resulting solution was stirred for 1 week at 25 °C. The reaction mixture was washed with 5% sodium bicarbonate and water and then dried over sodium sulfate. The solvent was evaporated and the residue chromatographed on alumina eluting with 1:3 dichloromethane/hexane to give **9** as an oil (0.57 g, 54% yield): ^1H NMR δ 7.44–7.53 (5 H, m), 5.00–5.20 (1 H, m), 3.90 (2 H, s), 3.30–3.50 (1 H, m), 3.10–3.20 (2 H, m), 2.00–2.20 (2 H, m), 1.99 (3 H, s), 1.20–1.95 (4 H, m), 1.58 (1 H, exchangeable, s); IR (KBr) 1725, 1268 cm^{-1}; MS (m/z) 276 (M^+ + 1).

Bao Gong Teng A, 6-*exo*-(Acetyloxy)-8-azabicyclo-[3.2.1]octan-2-*exo*-ol (1). To a suspension of 5% Pd/C (0.5 g) in 10 mL of ethanol was added *N*-benzyl Bao Gong Teng A (**9**) (0.5 g, 1.8 mmol) in 10 mL of ethanol. The mixture was pressurized with 3 atm of hydrogen gas. After the mixture had stirred for 4 h at 60 °C, the catalyst was removed by filtration and was washed with ethanol. The combined filtrate and washings were distilled in vacuo to remove the solvent. The resulting residue (0.32 g) was purified by chromatography on alumina, eluting with 1:3 dichloromethane/hexane to afford the target compound Bao Gong Teng A (**1**) (0.25 g, 74% yield) as a light yellow oil: ^1H NMR δ 5.15 (1 H, dd, J = 7.8, 2.2 Hz), 3.40–3.56 (2 H, m), 3.30 (1 H, m), 2.85 (2 H, exchangeable, s), 2.00 (3 H, s), 1.40–1.95 (6 H, m) [lit.[15] ^1H NMR δ 5.0–5.25 (1 H, dd, J = 8, 4 Hz), 3.35–3.75 (2 H, m), 3.15–3.35 (1 H, m), 2.5–3.0 (2 H, exchangeable, s), 2.05 (3 H, s), 0.65–2.4 (6 H, m)]; MS (m/z) 186 (M^+ + 1); $[\alpha]^{25}_D$ = 0° (c 0.10 in $CHCl_3$). The benzoic acid salt of **1** crystallized as needles (acetone), mp 158–159 °C (lit.[15] mp 152–154 °C).

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